(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 462 663 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **27.09.95** (51) Int. Cl.[6]: **C07F 9/38**

(21) Application number: **91201490.9**

(22) Date of filing: **14.06.91**

(54) Improved process for preparing salts of 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid (ABP).

(30) Priority: **20.06.90 US 540997**

(43) Date of publication of application:
27.12.91 Bulletin 91/52

(45) Publication of the grant of the patent:
27.09.95 Bulletin 95/39

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 402 152

DATABASE WPIL, accession no. 90-288402 [38], Derwent Publications Ltd, London, GB; & SU-A-1 544 775 (MOSCOW LOMONOSOV UNIV.)

(73) Proprietor: **MERCK & CO. INC.**
126, East Lincoln Avenue
P.O. Box 2000
Rahway
New Jersey 07065-0900 (US)

(72) Inventor: **Kieczykowski, Gerard R.**
248 W. Dudley Avenue
Westfield, NJ 07090 (US)

(74) Representative: **Thompson, John Dr. et al**
Merck & Co., Inc.
European Patent Department
Terlings Park
Eastwick Road
Harlow, Essex CM20 2QR (GB)

EP 0 462 663 B1

Description

This invention relates to an improved process for making 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid (ABP)or salts thereof, where the end product is obtained in pure form and high yield, and which avoids the use of a strongly-acidic hydrolysis medium.

It is known according to U.S. Patent 4,407,761 to Henkel Kommanditgesellschaft to prepare 4-amino-1-hydroxy-butylidene-1,1-bisphosphonic acid by bisphosponating an aminocarboxylic acid with phosphonating reactants and then quenching the reaction mixture by addition of a strong non-oxidizing acid, preferably concentrated hydrochloric acid, with heating, to hydrolyze the formed phosphorous intermediates to final product. However, problems result from this reaction because the bisphosphonation reaction mixture does not remain homogeneous and local solidification occurs. This solidification causes variable yields, which in part results from the exothermic nature of the reaction due to the development of "hot spots". Moreover, to make the sodium salt, utilizing the prior art processes, requires isolation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and an additional step to convert this to the monosodium salt. Further, the use of concentrated hydrochloric acid in the quench, whose fumes present an environmental problem, is also required.

Furthermore, U.S. Patent 4,922,007 to G. R. Kieczykowski, et al. (assigned to Merck & Co., Inc.) discloses the use of methanesulfonic acid to overcome the non-homogeneity and solidification problems associated with the bisphosphonation phase, but utilizes a non-pH controlled water quench which leads to the presence of a strongly acidic and corrosive hydrolysis mixture which requires the use of expensive glass reaction vessels with their inherent pressure limitations.

The present invention solves these problems by the use of methanesulfonic acid to allow the bisphosphonation reaction to remain fluid and homogeneous, and using a pH-controlled aqueous quench in the range of 4 to 10, followed by hydrolysis, which eliminates the need for concentrated hydrochloric acid in the quench. The present invention also eliminates the need to handle a corrosive acidic product hydrolysis mixture, such that stainless steel hydrolysis equipment rather than glass equipment can be utilized. Glass equipment has inherent pressure limitations not possessed by stainless steel. This is a big advantage in the instant process since it has been found that, by conducting the hydrolysis under pressure, the hydrolysis rate can be significantly increased.

It has been found that, in the quench, a pH above 10 leads to lower yields due to formed intermediates which resist hydrolysis, and a pH below 4 leads to much longer hydrolysis times. Further, it has been found that ABP is unstable at a pH above 8, thus limiting the reaction times and hydrolysis times at higher pHs.

By this invention, there is provided a process for the preparation of a salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid which comprises:

(a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulfonic acid;

(b) contacting the resulting mixture from Step (a) with an aqueous hydrolysis mixture, and

(c) recovering said salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid characterised in that the pH of the aqueous hydrolysis mixture is maintained in the range 4 to 10 during step (b).

The reaction can further be conducted controlling the pH during the aqueous quench in a narrow range i.e. 6-8, maintaining the temperature between 0-20 °C, and then heating the hydrolysis mixture at 50 °C - reflux, or under pressure for a sufficient time to insure complete hydrolysis to the titled product.

The invention involves the bisphosphonation of an aminoalkane carboxylic acid with phosphonating reactants in the presence of methanesulfonic acid, quenching the reaction mixture with an aqueous hydrolysis mixture, maintaining the pH at 4 to 10, hydrolyzing the phosphorus intermediates, formed in the quench procedure, and recovering a salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid. Such salts can be crystallized directly from the reaction mixture in about 90% yield after the pH controlled hydrolysis, for example for the sodium salt the pH may be adjusted to about 4.3 and said sodium salt obtained with no further purification necessary

The aminoalkane carboxylic acid used is 4-aminobutyric acid. The bisphosphonation reaction generally takes place at temperatures of from 45 ° to 125 °C., preferably at about 65 °C.

Generally 1 to 3, preferably 2.0 moles of H_3PO_3 and generally 1 to 5.0, preferably 4.0 mols of PCl_3 are used per mol of aminocarboxylic acid. Smaller amounts of 4-aminobutyric acid can be used which limits the formation of ABP dimers and decreases the necessary hydrolysis times. If desired, inert organic diluents, which do not solubilize the reaction product, particularly helped or chlorinated hydrocarbons, such as chlorobenzene, tetrachloroethane, tetrachloroethylene and trichloroethylene can be used in the reaction with methanesulfonic acid.

Following the reaction to form the acid, the reaction is quenched, i.e. drowned into an aqueous hydrolysis mixture. The conditions of the quench are such that pH is controlled in the range of pH 4 to 10, and preferably the pH is controlled in a narrow pH region, i.e. 6-8. By controlling the pH in this manner, it has been found that the yield of ABP can be maximized.

The aqueous hydrolysis mixture can contain basic materials or buffering agents.

Representative examples include sodium, potassium and lithium hydroxides, carbonates, bicarbonates, dihydrogen phosphates, hydrogen phosphates, borates, oxalates, tartrates, phthalates, phosphorous acid salts, and the like, and mixtures thereof.

Preferred is where the hydrolysis mixture is a buffered solution, preferrably a phosphate or bicarbonate buffered solution in the range pH 6-8.

The pH of the resulting quench mixture can also be controlled during the hydrolysis drown by the simultaneous addition of a basic reagent, e.g. sodium hydroxide.

The temperature of the quench is carried out in the range of 0-90 °C, and preferably 0-20 °C.

The required time of the quench drowning procedure will vary according to the volumes used.

Following the pH-controlled, temperature-controlled quench, the resulting mixture is stirred and heated in the temperature range of 50 °C to reflux and preferably at the reflux temperature of about 105-110 °C to complete and insure complete hydrolysis.

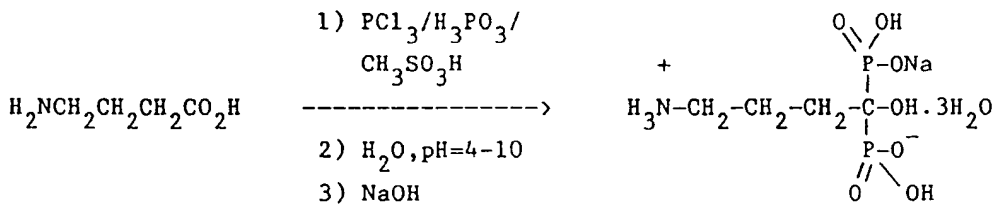
The volume ratio of the reaction mixture from the phosphonation Step (a) to the volume of the aqueous hydrolysis mixture in the quench Step (b) is about 1 to 5.

Alternatively, the hydrolysis mixture can be partially concentrated to about half the original volume, by distillation at atmospheric or reduced pressure, diluted with water to about the original volume and then refluxed. This procedure substantially reduces the hydrolysis time.

As a further alternative, the hydrolysis mixture can be heated at 110-165 °C in a closed vessel under pressure. This also substantially reduces the hydrolysis times.

It should be noted that a pH above about 7-8, the product ABP starts to undergo degradation with resultant yield loss, and thus preferably the desired hydrolysis workup procedure should be carried out in the pH range 6-8.

The reaction is schematically represented as follows:



$C_4H_9NO_2$

MW 103.12

$C_4H_{12}NNaO_7P_2 . 3H_2O$

MW 325.13

4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate described here is useful as a pharmaceutical composition and for the treatment or prevention of diseases involving bone resorption. Such diseases as hypercalcemia of malignancy, Paget's disease, and osteoporosis are advantageously treated with 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate made according to the process of the present invention.

Other pharmaceutically acceptable salts, such as for example the calcium , potassium salts, can be prepared according to the processes of the present invention and such processes are included within the scope thereof.

The following Description is illustrative of the prior art and the Examples are illustrative of the practice of the invention.

DESCRIPTION 1

Non-pH-Controlled Hydrolysis:
Preparation of 4-amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt trihydrate

Bisphosphonation Reaction Phase

A 250 mL flask was fitted with a mechanical stirrer, a thermocouple, an addition funnel and a reflux condenser through which is circulated -20 °C brine. The system was connected to a caustic scrubber which places a back pressure of 0.5-1 psig on the system. The system was flushed with nitrogen and charged with 20 g (0.19 mol) of aminobutyric acid, 80 mL of methanesulfonic acid, and 24 g (0.29 mol) of phosphorous acid. For larger scale operations, the methanesulfonic acid can be charged first, followed by the 4-aminobutyric acid and phosphorous acid. Upon mixing, the heat of neutralization and solution increased the reaction temperature to 75 °C. The suspension was aged for 15 minutes at 70-75 °C resulting in a clear colorless solution. The solution was cooled to 35 °C and phosphorus trichloride (PCl_3), 40 mL (0.46 mol) was added cautiously over 20 minutes. The reaction was then heated to 65 °C and aged at that temperature for 20 hours. The reaction should not be allowed to get much above 65 °C. The reaction becomes self-heating above 85 °C and under adiabatic conditions the temperature will increase steadily. At about 150 degrees an exotherm accompanied by a large pressure release occurs. It is therefore recommended that the reaction be immediately quenched into cold water if the temperature reaches 85 °C.

Quench; Hydrolysis

The reaction was then cooled to 25 °C and added to 200 mL of deionized water over 5 minutes. The flask was rinsed with an additional 100 mL of water and the combined strongly-acid solution (pH less than zero) aged at 95-100 °C for 5 hours. The reaction was cooled to 20 °C and maintained at 20-25 °C while the pH was adjusted to 4.3 with ca. 80 mL of 50% NaOH. The resulting white suspension was then cooled to 0-5 °C and aged for 1 hour. The pH was readjusted to 4.3 if necessary and the suspension aged at 0-5 °C for an additional 2 hours. The product was collected by filtration, then washed with 2 x 50 mL of cold (0-5 °C) water and 100 mL of 95% EtOH. The yield after air drying at 40 °C to constant weight was 56.4 g (90%).

EXAMPLE 1

Use of pH-Controlled Hydrolysis

4-aminobutyric acid	20 g
methanesulfonic acid	160 ml
phosphorous acid	32 g
phosphorus trichloride	80 ml

Bisphosphonation Reaction Phase

The above reagents were mixed and heated at 65 °C for 5 hours analogously according to the procedure of Description 1.

Quench; Hydrolysis

The reaction mixture was quenched over 35 minutes by adding dropwise to a solution of 10 g Na_2HPO_4 in one liter of water, at pH = 7.0. The pH of the quench was maintained between 6.0 and 7.0 by simultaneously adding 25% sodium hydroxide and maintained below 25 °C by cooling with ice. Once the quench was complete, the pH was adjusted to 7.0 and the solution concentrated to 1080 ml by atmospheric distillation (100-104 °C) over 3 hours. At this point, the reaction was subdivided into 2 parts, A and B.

A, being 630 ml, was concentrated further to 450 ml after adjusting the pH to 4.3. The solution was aged overnight at ambient temperature during which time the product crystallized. The suspension was aged at 0 °C for 2 hours then filtered, washed with 100 ml of cold water, 100 ml of 1:1 water/ethanol, and

100 ml of 100% ethanol and dried, yielding 20.5 g (56% yield).

B, being 450 ml, was treated by refluxing an additional 16 hours before adjusting the pH to 4.3 and concentrating to 300 ml. The product was isolated as above providing 16.5 g. (63% yield) of ABP.

This Example illustrates that the above bisphosphonation reaction, in conjunction with a buffered quench, minimized the ABP dimers and phosphonates which are more difficult to hydrolyze, thus reducing the required hydrolysis times.

EXAMPLE 2

4-aminobutyric acid	60 g
methanesulfonic acid	240 ml
phosphorous acid	48 g
phosphorus trichloride	120 ml

Bisphosphonation

The reaction was run analogously using the procedure described in : Description 1 (65 °C overnight) with the above quantity of reagents. The total reaction volume was 430 ml. The reaction was subdivided into aliquots prior to quenching.

Quench; Hydrolysis

Aliquots were quenched into 100 ml of water while simultaneously adding 20% sodium hydroxide to maintain a pH of 6-10. The pH was adjusted to different values between 4-10 and the reaction refluxed for an appropriate amount of time to produce and isolate product (see below). The pH was then adjusted to 7 and the solution filtered. The pH was then adjusted to 4.3 and the solution aged overnight during which time the product crystallized. The suspension was then aged at 0 °C for 2 hours and filtered. The cake was washed with water then ethanol and dried.

Aliquot	pH	Time Refluxed[1]	Yield
50 ml	11	1 day	9.6 g (44%)
46 ml	10	2 days	11.4 g (56%)
20 ml	9	2 days	5.0 g (54%)
23 ml	8	6 days	6.8 g (66%)
21 ml	7	10 days	6.6 g (72%)
21 ml	7	10 days	7.2 g (78%)[2]
21 ml	7	5 days	7.0 g (75%)[3]
21 ml	7	42 hrs.[4]	2.4 g (65%)
21 ml	6	11 days	6.8 g (74%)
ml	5	days[5]	g (%)
ml	4	days[5]	g (%)
ml	3	days[5]	g (%)

[1] Temperature between 105-110 °C at 1 atmosphere.

[2] Used an equal volume of ethanol in the crystallization.

[3] Partially concentrated by atmospheric distillation to about half the volume, diluted with an equal volume of water and then refluxed.

[4] After quenching, refluxed at 140 °C in a closed pressure vessel.

[5] After 12 days, the hydrolysis mixture was analyzed by phosphorus NMR. The pH = 5 and pH = 4 reactions indicated incomplete hydrolysis mixtures. The pH = 3 reaction indicated incomplete hydrolysis mixture and significantly longer hydrolysis times projected for its completion.

This Example illustrates that the product can be quenched and hydrolyzed under neutral and basic conditions in good yield, but that at the higher pH values, the yields are lower due to competing degradation of the product.

Claims

1. A process for the preparation of a salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid which comprises:
   (a) reacting 4-aminobutyric acid with a mixture of phosphorous acid and PCl_3 in the presence of methanesulfonic acid;
   (b) contacting the resulting mixture from Step (a) with an aqueous hydrolysis mixture,
   (c) recovering said salt of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid; characterised in that the pH of the aqueous hydrolysis mixture is maintained in the range 4 to 10 during step (b).

2. The process of claim 1 wherein the pH is maintained in Step (b) in the range of 6-8.

3. The process of Claim 1 further comprising heating the resulting mixture from Step (b) in the range of 50 °C to the boiling point.

4. The process of Claim 1 wherein said Step (b) is conducted at a temperature of from 0 °C to 90 °C.

5. The process of Claim 4 wherein said temperature is 0-20 °C.

6. The process of Claim 1 wherein said aqueous hydrolysis mixture in Step (b) is a phosphate buffer.

7. The process of Claim 6 wherein said buffer comprises monosodium dihydrogen phosphate and disodium monohydrogen phosphate.

8. The process of Claim 1 wherein 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium salt trihydrate is recovered.

9. The process of any of claims 6 to 8 wherein step (a) is carried out at a temperature of about 65 °C; and step (b) is carried out at a temperature of 0 to 20 °C and a pH maintained between 6 and 8 during the contacting, followed by heating the resulting mixture at boiling point.

Patentansprüche

1. Ein Verfahren zur Herstellung eines Salzes der 4-Amino-1-hydroxybutyliden-1,1-bisphosphonsäure, das umfaßt:
   (a) Umsetzen von 4-Aminobuttersäure mit einem Gemisch aus phosphoriger Säure und PCl_3 in Anwesenheit von Methansulfonsäure;
   (b) Inkontaktbringen des entstandenen Gemischs aus Schritt (a) mit einem wäßrigen Hydrolysegemisch,
   (c) Gewinnen des besagten Salzes der 4-Amino-1-hydroxybutyliden-1,1-bisphosphonsäure; dadurch gekennzeichnet, daß der pH-Wert des wäßrigen Hydrolysegemischs während Schritt (b) im Bereich von 4 bis 10 gehalten wird.

2. Das Verfahren nach Anspruch 1, bei dem der pH-Wert in Schritt (b) im Bereich von 6-8 gehalten wird.

3. Das Verfahren nach Anspruch 1, das weiter das Erhitzen des entstandenen Gemischs aus Schritt (b) im Bereich von 50 °C bis zum Siedepunkt umfaßt.

4. Das Verfahren nach Anspruch 1, bei dem besagter Schritt (b) bei einer Temperatur von 0 °C bis 90 °C durchgeführt wird.

5. Das Verfahren nach Anspruch 4, bei dem besagte Temperatur 0-20 °C beträgt.

6. Das Verfahren nach Anspruch 1, bei dem besagtes wäßriges Hydrolysegemisch in Schritt (b) ein Phosphatpuffer ist.

7. Das Verfahren nach Anspruch 6, bei dem besagter Puffer Mononatriumdihydrogenphosphat und Dinatriummonohydrogenphosphat umfaßt.

8. Das Verfahren nach Anspruch 1, bei dem Mononatrium-4-amino-1-hydroxybutyliden-1,1-bisphosphonsäuretrihydrat-Salz gewonnen wird.

9. Das Verfahren nach einem der Ansprüche 6 bis 8, bei dem Schritt (a) bei einer Temperatur von ungefähr 65 °C durchgeführt wird; und Schritt (b) bei einer Temperatur von 0 bis 20 °C und einem zwischen 6 und 8 gehaltenen pH-Wert während des Inkontaktbringens durchgeführt wird, gefolgt von Erhitzen des entstandenen Gemischs am Siedepunkt.

Revendications

1. Procédé pour la préparation d'un sel de l'acide 4-amino-1-hydroxybutylidene-1,1-bisphosphonique, ce procédé comportant les points suivants ;
   (a) on fait réagir l'acide 4-aminobutyrique avec un mélange d'acide phosphoreux et de PCl_3 en présence d'acide méthane-sulfonique ;
   (b) on met au contact le mélange provenant de l'étape (a) avec un mélange d'hydrolyse aqueux.
   (c) on recueille ledit sel de l'acide 4-amino-1-hydroxybutylidène-1,1-bisphosphonique ;
   le procédé étant caractérisé en ce que le pH du mélange aqueux d'hydrolyse est maintenu dans le domaine de 4 à 10 lors de l'étape (b).

2. Procédé selon la revendication 1, où le pH est maintenu dans l'étape (b) dans le domaine de 6-8.

3. Procédé selon la revendication 1, qui comporte en outre le chauffage du mélange résultant de l'étape (b) dans le domaine allant de 50 °C au point d'ébullition.

4. Procédé selon la revendication 1, où ladite étape (b) est réalisée à une température de 0 °C à 90 °C.

5. Procédé selon la revendication 4, où ladite température est de 0 à 20 °C.

6. Procédé selon la revendication 1, où ledit mélange aqueux d'hydrolyse dans l'étape (b) est un tampon phosphate.

7. Procédé selon la revendication 6, où ledit tampon comporte du dihydrogénosphosphate monosodique et du monohydrogénophosphate disodique.

8. Procédé selon la revendication 1, où l'on recueille le sel trihydrate monosodique de l'acide 4-amino-1-hydroxybutylidéne-1,1-bisphosphonique.

9. Procédé selon l'une quelconque des revendications 6 à 8, où l'étape (à) est réalisée à une température d'environ 65 °C ; et l'étape (b) est réalisée à une température de 0 à 20 °C et à un pH maintenu entre 6 et 8 pendant le contact, puis en chauffant le mélange résultant au point d'ébullition.